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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/655,272	09/05/2000	Eric Honore	1383-00	8032

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/655,272	HONORE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,32-35,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 32-35, 37-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The previous Office Action of 19 April 2004 is hereby vacated. For Applicant's records, please use the mail date of the current office action.

Status of Application, Amendments and/or Claims

The amendment of 26 September 2003 has been entered in full. Claims 32-35 and 37-38 are amended. Claims 9-31 and 36 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 8, 32-35, and 37-38 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 3-5 of the previous Office Action (25 March 2003) are *withdrawn* in view of the amended specification (26 September 2003)

2. The rejection of claims 8-9, 31-35, and 37-38 under 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 5-10 of the previous Office Action (25 March 2003) is *withdrawn in part* in view of the cancelled claims and the amendment to claim 33 (26 September 2003). Please see 35 U.S.C. § 112, first paragraph, below.

3. The rejection of claims 9, 31-33, and 37-38 under 35U.S.C. § 112, first paragraph (written description) as set forth at pg 10-12 of the previous Office Action (25 March 2003) is *withdrawn in part* in view of the cancellation of claim 9 (26 September 2003). Please see 35 U.S.C. § 112, first paragraph, below.

4. The rejections of claims 8-9, 31-35, and 37-38 under 35 U.S.C. § 112, second paragraph as set forth at pg 12-15 of the previous Office Action (25 March 2003) is *withdrawn in part* in

view of the amended and cancelled claims (26 September 2003). Please see section on 35 U.S.C. § 112, second paragraph, below.

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 32-33 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening substances capable of modulating the potassium current of a purified TRAAK potassium channel protein, which comprises: (a) transferring the purified nucleic acid sequence of SEQ ID NO: 1, the nucleic acid sequence comprising nucleotides 284-1477 of SEQ ID NO: 1, or the nucleic acid sequence that encodes the channel consisting of the amino acid sequence of SEQ ID NO: 2 or 4 into a cellular host; (b) culturing said host under suitable conditions for expression of said channel; (c) bringing into contact the substance to be screened with said host expressing said channel; and (d) measuring the potassium current of said channel, wherein an increase or decrease in potassium current indicates modulation of activation of said channel, does not reasonably provide enablement for a method for screening substances capable of modulating the potassium current of a purified TRAAK channel protein which comprises: (a) transferring a purified nucleic acid sequence or a functionally equivalent derivative that encodes TRAAK potassium channel protein; (b) culturing the host under conditions for expression of TRAAK potassium channel; (c) reacting selected amounts of the substance to be screened with the cellular host; and (d) measuring the current of the substance to be screened on a potassium channel's current expressed by the cellular host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection under 35 U.S.C. § 112, first paragraph is set forth at pg 5-10

of the previous Office Action (25 March 2003) and at pg 4-7 of the Office Action of 19 June 2002. Please see points (i)-(iii) below.

Applicant's arguments (26 September 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive.

(i) Applicant asserts that in light of the teachings of the specification, which disclose not only the nucleic and amino acid sequence for the TRAAK channel proteins, but also specific structural and functional components of the TRAAK channel proteins, the specification is fully enabled. Applicant argues that the electrophysiological properties of both TREK-1 and TRAAK channels are activated by a tension applied to the plasma membrane (pg 16 of specification). Applicant contends that TRAAK and TREK-1, which are both members of a TWIK-1 potassium channel family, have been identified as containing 4 transmembrane segments and 2 P domains. Applicant indicates that the structural and functional characteristics of TREK-1 and TRAAK-1 proteins have been clearly defined by the specification. Applicant states that TRAAK is activated by polyunsaturated acids and riluzole. Applicant asserts that one skilled in the art can practice the invention with little experimentation because of the detailed structural and functional characteristics of TRAAK and TREK-1 proteins. Applicant submits that one skilled in the art can simply use the sequence in the instant specification to detect homologous sequences in public DNA data libraries. Applicant continues to list a series of steps to isolate a protein at pg 8 of the response and argues that these steps are not considered to be undue experimentation by those of skill in the art. Applicant states that the derivative can be screened with polyunsaturated acids or riluzole.

Applicant's arguments been fully considered but are not deemed to be persuasive for the following reasons. The specification of the instant application does not teach screening for substances capable of modulation of potassium channel activation using any potassium channels other than full-length TREK-1 (SEQ ID NO: 4) and TRAAK (SEQ ID NO: 2). The specification only teaches screening for substances by transferring a purified nucleic acid sequence represented by SEQ ID NO: 1 or nucleic acids 284-1477 of SEQ ID NO: 1 (which encode the mature protein) into a cellular host (pg 14-19). Undue experimentation would be required of the skilled artisan to generate and screen all possible TRAAK channel proteins and derivatives for activity. The claims read on any TRAAK channel protein and any functional and non-functional derivatives, which can encompass proteins with diverse amino acid and nucleic acid sequences. Although the specification teaches that a functional equivalent derivative includes those with a sequence comprising a modification and/or suppression and/or addition of one or more amino acids as long as the modification/suppression/addition does not modify the properties of the TRAAK channel, the specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such trial and error experimentation is considered undue. Although Applicant submits that the nucleic acid/protein synthesis and screening processes are routine, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one or ordinary skill in the art to determine, without undue experimentation, the positions in the TRAAK protein and DNA which are tolerant to change and the nature and extent of changes that can be made in these positions. A specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive (MPEP § 2164.06).

(ii) Applicant argues that certain amino acid substitutions are conservative because in families of homologous proteins they are found to occur more often than others. Applicant asserts that the claims are drawn to substitutions which are conservative, owing to the fact that function as a potassium transport (TRAAK type potassium channel transport) must be retained. Applicant cites *In re Goffe* to emphasize that to limit the claims to the specific sequence disclosed and described in the specification would fail to adequately protect Applicant's invention. Applicant also cites *In re Colianni*, 195 USPQ 150 (CCPA 1977), *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1998), and *In re Bundy* 209 USPQ 48, 51-52 (CCPA 1991).

Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with

functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the TRAAK polynucleotides to make biologically active derivatives without resorting to undue experimentation to determine what the specific biological activities of the derivatives are.

Furthermore, the fact pattern of the instant application is not inconsistent with *In re Colianni*, 195 USPQ 150 (CCPA 1977), *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Circ. 1998), or *In re Bundy* 209 USPQ 48, 51-52 (CCPA 1981). Again, although the specification in the instant application teaches art-recognized procedures for producing and screening for active TRAAK proteins and derivatives, this is not adequate guidance as to the nature of active TRAAK derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort

to trial and error experimentation to generate the infinite number of TRAAK proteins and derivatives, as recited in the claims, and to screen them for a desired activity. Such trial and error is considered undue. Additionally, undue experimentation would also be required of the skilled artisan to determine the biological activity that is associated with the claimed TRAAK proteins and derivatives. The Examiner is unable to examine the fact pattern or comment on Applicant's citation of *In re Goffe* because the Examiner cannot readily determine which citation and which page Applicant is referring to (*In re Goffe*, 191 USPQ 429 (CCPA 1976) or *In re Goffe*, 188 USPQ 131 (CCPA 1975). It is also noted to Applicant that the Examiner is not required to address every Wands factor and the most pertinent factors have been addressed in the instant application (see concluding paragraph below).

The instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The only disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The Board found that there was no reasonable correlation between the scope of exclusive right desired by Applicant and the scope of enablement set forth in the patent application. Even though Applicant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation.

Clearly, a single disclosed sequence does not support claims to utilizing any nucleic acid encoding a TRAAK potassium channel protein or functionally equivalent derivative, given the lack of guidance regarding what sequences would the desired biological activity.

(iii) Additionally, regarding claims 37-38, a large quantity of experimentation would be required by the skilled artisan to identify and screen all possible substances capable of preventing or treating heart disease or central nervous system disease in mammals. The specification's general discussion of screening for substances (pg 8-10) constitutes an invitation to experiment by trial and error. Since the claims encompass such structurally and functionally diverse substances as antibodies, nucleic acid molecules, proteins, and organic or inorganic compounds, the skilled artisan must resort to trial and error experimentation to identify and generate the infinite number of substances, and to screen them for a desired activity (e.g., preventing or treating heart disease or central nervous system diseases). Such trial and error is considered undue. There is little guidance provided in the specification as which substances are capable of treating heart disease or central nervous system disease in a mammal. Although the specification discloses examples of substances that could be screened (fatty acids and riluzole; pg 17-19), there is little guidance to indicate that these substances prevent or treat all possible heart disease conditions or all possible central nervous system diseases. Also, regarding the recitation of "preventing" a disease in claims 37-38, the specification does not disclose preventing any heart diseases or central nervous system diseases by administration of a screened substance to a mammal. The term "prevent" is interpreted as meaning that an activity will not occur, i.e. heart disease will not occur or central nervous system diseases will not occur. Undue experimentation would be required of the skilled artisan to identify a screened substance with the desired activity

and to determine the quantity of screened substance to be administered, the best route of administration, and the duration of treatment. A large quantity of experimentation would also be required by the skilled artisan to determine which specific heart diseases and central nervous system diseases can be treated by a substance. One skilled in the art would not be able to predict from the instant specification that a screened substance would be able to treat all possible heart diseases and central nervous system diseases, such as acute bradycardia, stroke, Alzheimer's disease, blunt trauma, and Parkinson's disease, because these diseases have different pathophysiologies.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and to screen all possible mechanosensitive potassium channels and their derivatives for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities, and the breadth of the claims which fail to recite any limitations as to the proteins to be screened and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 32-33 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for screening substances capable of modulating the potassium current of a purified TRAAK channel protein which comprises: (a) transferring a purified nucleic acid sequence or a functionally equivalent derivative that encodes TRAAK potassium channel protein; (b) culturing the host under conditions for expression of TRAAK potassium channel; (c) reacting selected amounts of the substance to be screened with the cellular host; and (d) measuring the current of the substance to be screened on a potassium channel's current expressed by the cellular host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection under 35 U.S.C. § 112, first paragraph is set forth at pg 10-12 of the previous Office Action (25 March 2003).

Applicant's arguments (26 September 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive.

(i) Applicant asserts that the novel TRAAK protein and the functionally equivalent derivatives have a demonstrated and particular biophysical property which cab be used to screen out non-functional derivative proteins of TRAAK. Applicant contends that the data in cloning libraries, along with specific structural and functional characteristics of TRAAK, allow one skilled in the art to find functionally equivalent derivatives thereof. Applicant submits that at the

time the specification was filed, the claimed invention needs to be capable of being reduced to practice (*Oregon Health and Science Univ. v. Vertex Pharm. Inc.*, 66 USPQ2d 1381 (D.C. Ore 2002).

Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. Applicant has not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polynucleotides and proteins recited in the claims. Applicant's arguments have been considered but are not found to be persuasive because the broad brush discussion of making and screening for TRAAK proteins and derivatives does not constitute a disclosure of a representative number of members. No such proteins or derivatives were made or shown to have activity. Only an isolated nucleic acid molecule consisting of the nucleotide sequence of SEQ ID NO: 1 or nucleotides 284-1477 of SEQ ID NO: 1 and a nucleic acid molecule which encodes a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 are disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants.

It is also noted that the fact patterns of the case cited by the Applicant (*Oregon Health and Science Univ. v. Vertex Pharm. Inc.*, 66 USPQ2d 1381 (D.C. Ore 2002).
and of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. For example, in *Oregon Health and Science Univ. v. Vertex Pharm. Inc.* the main issue is patent validity regarding a correction to change inventorship rather than written description (which is one issue in the instant application).

(ii) Furthermore, regarding claims 37-38, the specification teaches that "the invention thus pertains to a chemical or biological substance capable of modulating the currents of a potassium channel according to the invention for the preparation of a drug that is useful in the prevention or treatment of diseases of the heart or nervous system in human or animal subjects, such as cardiac pathologies (arrhythmias) and vascular diseases, neurodegenerative diseases, especially those associated with ischemia and anoxia, endocrine diseases associated with defective hormone secretion and muscle diseases. (pg 9, lines 5-11). However, the specification does not teach any specific substances that are capable of preventing or treating heart disease or central nervous system disease in mammals. The brief description in the specification of a few examples of substances that could be screened (fatty acids and riluzole; pg 17-19) is not adequate written description of an entire genus of substances that treat heart disease or central nervous system disease in mammals.

The skilled artisan cannot envision all possible substances of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The detectable signal or signaling pathway itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only a specific substance that is capable of treating heart disease or central nervous system disease, but not the full breadth of the claim meets the written description

provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

12. Claims 8, 32-35, and 37-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 8, 32-35, and 37-38 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating how the effect or activity measured has to change in order to identify a substance. Would there be an increase in activity? A decrease? Does the result depend upon the type of substance administered? The basis for this rejection is set forth at pg 12-13 of the previous Office Action (25 March 2003) and at pg 8 of the Office Action of 19 June 2002.

Applicant's arguments (26 September 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons. Applicant asserts that claims 8,9, 31-35, and 37-38 have been amended to clearly relate back to the preamble. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, claims 8, 32-35, and 37-38 still do not recite a step that relates back to the preamble. For example, the following phrase could be added after part (d) of each independent claim: "wherein an increase or decrease in potassium current indicates modulation of activation of said channel".

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
08 April 2004

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